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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,341	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that there has been a change in examiner assignment with regard to the prosecution of this application.

2. Acknowledgement is made of applicants election of Group I, drawn to immunotherapeutic compositions. The traversal is on the grounds that the restriction is improper because it would not be an undue burden to search the subject matter of Group II because Group II is dependent upon the compositions of Group I. After review of the literature with respect to Group I, it was found that applicant's arguments were persuasive. The restrictions requirement of the Paper mailed August 2004 has been withdrawn, but the election of species requirement is maintained.

3. Claim 27 has been amended. Claims 1-33 are pending. Claims 10, 11, 22 and 26, drawn to non-elected species, are withdrawn from consideration. Claims 1-9, 12-21, 23-25 and 26-33 are pending and examined on the merits.

Claim Objections

4. Claim 1 is objected to because of the following informalities: The claim consists of two sentences. For purpose of examination, the first period will be interpreted as a comma. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9, 12-21, 23-25 and 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1, 7, 12 and 29 are vague and indefinite in the recitation of "interaction between a receptor and its ligand, in the receptor tyrosine kinase system (RTK), this combination includes:", "interaction between a receptor and its ligand, in the system of receptor tyrosine kinases (RTK), this combination including:" and "interaction between a receptor and its ligand, in the system of receptor protein tyrosine kinases (RTK), this combination includes:" and "interaction between a receptor and its ligand, in the receptor tyrosine kinase (RTK) system, this method including the treatment...". It is unclear if the recited antibodies and ligands following these phrases serve to qualify the entire genus of claimed combinations, or if the recited antibodies and ligands following said phrases are to be applied only to in the case that the receptors and ligands are of the tyrosine kinase systems. For purpose of examination, both alternatives will be considered.

Applicant is advised to use uniform language to avoid confusion in the claimed subject matter. Applicant would be cautioned against using variants to receptor tyrosine kinase (RTK), such as receptor tyrosine kinase system and receptor protein tyrosine kinase.

(B) Claims 1, 7 and 12 are vague and indefinite in the recitation of "system" with regard to protein tyrosine kinases. It is unclear if "system" intends to encompass receptors and ligands of other proteins upstream and downstream of the RTK signaling pathway.

(C) It is unclear how claims 3 and 4 further modify claim 2. Claim 2 specifies that the RTK is EGF, thus both the antibody and vaccine of claim 1 must be RTK. Claim 3 embodies the composition of claim2 wherein the vaccine is directed against the EGF receptor. If the vaccine is the EGF receptor, as required by claim 2, it would be inherent that the vaccine would be "directed against" the EGF receptor. Claim 4 embodies the combination of claim 2, where the antibody is an antibody against the EGF receptor. For the reasons stated above, this would be inherent in the limitations of claim 2.

(D) The recitation of "antibody" in claims 13-21 [singular] lacks antecedent basis in claim 12 ["antibodies", plural]

(E) Claim 9 is vague and indefinite because it is unclear if the P64K and EGF proteins are conjugated together or if both P64K conjugates and EGF-a conjugates represent different genuses.

(F) Claim 27 has been amended to delete reference to claims 2-27, however the term "inclusive" is still present in the amended claims. It is unclear what the term "inclusive" is referring to.

(G) The recitation of "vaccines" in claim 31 lacks proper antecedent basis in claims 1, 7 and 12. The recitation of "antibodies" in claim 31 lacks proper antecedent basis in claims 1 and 7. The recitation of "first stage" and "second stage" in claims 32 and 33 lacks proper antecedent basis in claims 1, 7, 12 and 29.

(H) Claims 32 and 33 are vague and indefinite because it is not clear what antibody and vaccine is being referred to by the recitation of "this" antibody and "this" vaccine.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-9, 12-21, 23-25 and 26-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods vaccines in which the active principle is EGF conjugated to a foreign T-helper cell peptide, such as tetanus toxoid, for the induction of antibody response against EGF which is a neutralizing antibody response, does not reasonably provide enablement for methods or compositions requiring vaccines comprising as the active agent large protein ligands or protein receptors or immunotherapy compositions comprising IOR R3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) As drawn to combinations beyond a vaccine directed against EGF.

The instant claims encompass combinations of antibodies which bind to protein tyrosine kinase receptors or antibodies which bind to tyrosine kinase receptor ligands, wherein the administration of said antibodies is combined with a vaccine in which the active principle is a protein tyrosine kinase receptor or a protein tyrosine kinase receptor ligand. Both the art and the instant specification teach that it is necessary to provide an foreign T-cell helper epitope, usually

from an immunogenic bacterial antigen, in order to induce a humoral immune response against a "self" antigen (Grimes et al, US 6,783,761). The prior art also teaches vaccines which elicit antibodies against EGF wherein EGF is conjugated to a foreign T-cell helper epitope (US 5,894,018). It is noted that EGF is a 53 amino acid peptide. Other tyrosine kinase receptor ligands and the tyrosine kinase receptors themselves are much bigger than EGF, for instance hepatocyte growth factor, or scatter factor, is a 723 amino acid ligand for its receptor c-met which is 1390 amino acids long; PDGF-B, is a 226 amino acid ligand responsible for neoplastic activity at the 1106 amino acid PDGF receptor; TGF-alpha, the ligand of claims 10, 11 and 26 is 159 amino acids. Fong et al (US 2003/0219380) teach that Protein tyrosine kinases (PTKs) such as EGFR, APMIS, HER2, PDGF-R and c-met are directly associated with the cell proliferative disorders and the development of cancers and are over-expressed in many tumors and/or persistently activated by autocrine loops. Fong et al teach that PTK over-expression and autocrine loop stimulation account for the most common and severe cancers. Thus, one of skill in the art would reasonable conclude that a vaccine which elicits an antibody which is capable of neutralizing the activity of the tyrosine kinase receptor ligand would be effective at interrupting the autocrine loop on which the cancer cells depend. One of skill in the art would also reasonable conclude that vaccine which elicit antagonistic antibodies that bound to the tyrosine kinase receptors and blocked the endogenous effect of the autocrine/paracrine ligands and did not activate the receptor upon binding would be effective at interrupting the autocrine loop on which the cancer cells which over express said receptors depend. The specification does not teach how to make a vaccine which would elicit an antagonistic antibody against a tyrosine kinase receptor, or a neutralizing antibody against a tyrosine kinase receptor ligand which was not a small peptide. The art teaches that conjugation of a small self peptide to a foreign T-cell helper epitope such as tetanus toxoid aids in the recognition of the fused peptide as "non-self". It is reasonable to conclude that the physical proximity of the peptide sequence to the "self" peptide is necessary for this recognition by the immune system. In the case of a larger tyrosine kinase receptor, or a larger tyrosine kinase receptor ligand, the amino acid sequence adjacent to the foreign peptide will be recognized as "non-self". However, there is no scientific basis for concluding that the processing of the entire protein comprising the foreign T-cell helper epitope by the host immune system will provide B-cell epitopes on antigen-presenting cells which would

allow for the activation of B-cells which would secrete an antibody having the required neutralizing action on a large PTK ligand, such as HGF, or having the ability to antagonize a PTK receptor, such as EGFR. These large ligands and receptors comprise many potential antigenic epitopes to which a antibody might bind, but only a limited number of said epitopes will provide a binding site for an antibody that will result in the necessary neutralization or antagonistic activity. For instance, Lokker et al (J Biol Chem, 1997, Vol. 272, pp. 33037-33044) teach that anti-PDGF receptor antibodies generated in a foreign host include antibodies which inhibited receptor phosphorylation and mitogenic response and antibodies which did not, such as 2A1E2 and 1B5B11 versus 2G4D10 and 2H7C5 (page 33039, second column, lines 14-21 and page 33040, first column, lines 8-17).

Gill et al (J Biol Chem, 1984, Vol. 259, pp. 7755-7760) teach that three types of monoclonal antibody generated against EGF receptors in foreign hosts have been described and include an IgM antibody which is an agonist for cell growth and competes with EGF for binding; a second group of Ab of different classes which are able to immunoprecipitate EGF receptors but do not effect EGF binding or elicits biological responses; and a third group of Ab block EGF binding to the EGF receptor, but the antibodies themselves have a complex effect on cell growth which appear to mediate the stimulatory effect of EGF (page 7755, second column, lines 2-26). It can be concluded that the interaction of an antibody with a large protein receptor is complex, because binding at different epitopes of said receptor will elicit different biological effects on said receptor. By the same reasoning, the interaction between an antibody and a large protein is also complex: the antibody may bind to an area of the protein which would not inhibit contact between the ligand and the receptor.

While the instant specification is enabled for the administration of an antibody which is antagonistic to the receptor and inhibits the mitogenic effect of the receptor in the presence of the natural ligand, and also for the administration of a neutralizing antibody which binds to a PTK ligand, wherein the antibodies have been pre-screened for biological activity in vitro, the specification is not enabling for how to make said antibodies in a patient by eliciting an immune response against the receptor or large ligand. Given the lack of teachings in the specification for how to elicit the required antibodies in vivo by administration of the described vaccine, one of

skill in the art would be subject to undue experimentation in order to make the claimed immunogenic combinations and carry out the claimed methods.

(B) As drawn to the specific humanized antibody of IOR R3

The specification lacks an enabling disclosure of how to make the hybridoma or other cell line which secretes the an antibody which is exactly the same as the IOR R3 antibody. It is recognized in the art that exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies". It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies without a publicly available source of the cell line secreted the IOR R3 antibody.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:
(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:
(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
(d) the deposits will be replaced if they should become nonviable or non-replicable.
Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies B105 and B110 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibodies B105 and B110 as described in the specification and were in the applicant=s possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 7, 12 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Michaeli et al (WO9851337).

It is noted that metes and bounds of claims 1, 7, 12 and 29 cannot be determined because it is unclear if the entire claimed combination is required to be an antibody which binds PTK ligand or receptor with a vaccine that consists of the PTK receptor or ligand, or if these limitations are only applied to the interaction between a receptor and a ligand which happened to be a PTK receptor and ligand. Because of the vague and indefinite claim language, alternative interpretations of the claim will be considered.

Claims 1 and 12 are drawn in part to a combination useful for immunotherapy wherein this combination has an effect on the growth and proliferation of cells, whose growths dependent upon the interaction between a receptor and its ligand. Claim 7 is drawn in part to a treatment combination useful for immunotherapy wherein this combination has an effect on the growth and proliferation of cells, whose growth s dependent upon the interaction between a receptor and its ligand.

Claim 29 is drawn in part to a method to control the growth and proliferation of cells whose growth is dependent upon the interaction between a receptor and its ligand.

Michaeli et al disclose compositions and immunological methods for the treatment of gastrin-dependent tumors. The method comprises the active or passive immunization of a patient with an anti-CCK-B/gastrin receptor immunogen or anti-CCK-B/gastrin receptor antibodies, wherein antibodies produced by the immunogens are specific against the CCK-B/gastrin receptor on tumor cells and block the growth-promoting effects of gastrin on the receptors and wherein the antibodies prevent the peptide hormones from binding to the CCK- B/gastrin receptors on gastrin-dependent tumor cells; thus, the growth of the tumor is arrested (page 4, lines 14-20 and page 5, lines 8-11). Michaeli et al disclose that if complete inhibition of gastrin binding to the receptor does not occur in the autocrine growth cascade, then the gastrin antagonists may be unable to block this mechanism of tumor growth promotion (page 4, lines 10-12). Michaeli et al disclose that in addition, the anti-CCK-B/gastrin receptor antibodies may be further conjugated to cytotoxic molecules such as cholera toxin, or to radioactive molecules labeled with a radionuclide, such as 1315I and131I, to enhance the killing of the tumor cells (page 6, lines 1-3). The conjugated antibodies fulfill the specific limitation of "combination", because the gastrin receptor is not a protein tyrosine kinase receptor and therefore not subject to the limitations of clauses a and b in claims 1, 7 and 12.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 7, 12 and 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michaeli et al (WO9851337).

Claim 30 embodies the method of claim 29 which includes the simultaneous treatment with agents against the RTK receptors and their ligands. Claim 31 embodies the method of claim 29 which includes the simultaneous treatment with vaccines and antibodies. Claim 32 embodies the method of claim 29 that includes the treatment in the first stage with this antibody and at a second stage with this vaccine. Claim 33 embodies the method of claim 29 that includes treatment at a first stage with this vaccine and at a second stage with this antibody.

Michaeli et al teach compositions and immunological methods for the treatment of gastrin-dependent tumors. The method comprises the active or passive immunization of a patient with an anti-CCK-B/gastrin receptor immunogen or anti-CCK-B/gastrin receptor antibodies, wherein the antibodies produced by the immunogens are specific against the CCK-B/gastrin receptor on tumor cells and block the growth-promoting effects of gastrin on the receptors and

wherein the antibodies prevent the peptide hormones from binding to the CCK- B/gastrin receptors on gastrin-dependent tumor cells; thus, the growth of the tumor is arrested (page 4, lines 14-20 and page 5, lines 8-11). Michaeli et al teach that the anti-CCK-B/gastrin receptor antibodies may be further conjugated to cytotoxic molecules such as cholera toxin, or to radioactive molecules labeled with a radionuclide, such as 1315I and131I, to enhance the killing of the tumor cells (page 6, lines 1-3). The conjugated antibodies fulfill the specific limitation of "combination", because the gastrin receptor is not a protein tyrosine kinase receptor and therefore not subject to the limitations of clauses a and b in claims 1, 7 and 12. Michaeli et al teach that if complete inhibition of gastrin binding to the receptor does not occur in the autocrine growth cascade, then the gastrin antagonists may be unable to block this mechanism of tumor growth promotion (page 4, lines 10-12). Michaeli et al do not specifically teach the induction of a neutralizing humoral response to gastrin in combination with the passive administration of anti-gastrin antibodies to a patient.

It would have been prima facie obvious at the time the claimed invention was made to administer anti-gastrin antibodies to a patient in conjunction with active immunization against gastrin to produce gastrin-neutralizing antibodies in vivo. One of skill in the art would have been motivated to do so through the statement of Michaeli et al teaching the necessity of the complete inhibition of the gastrin autocrine growth cascade. One of skill in the art would be motivated to use any combination of methods taught by Micheali et al to inhibit the autocrine growth cascade to block tumor growth in vivo. Regarding the specific embodiments of claims 30-33, it is well within the purview of one of skill in the art to determine the optimum sequence of administered therapeutic agents to achieve the maximum therapeutic benefit to a patient.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
2/3/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER